PERINATAL ASPHYXIA AND PSYCHOLOGIC SIGNS OF BRAIN DAMAGE IN CHILDHOOD

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AN UNSELECTED sample of newborn infants has been followed into childhood to study psychologic effects of perinatal asphyxia. This is the second report of the follow-up studies on the sample. In the first study by Apgar *et al.*,[1] oxygen content of heel blood was used as an index of asphyxia in the neonatal period, and tests for intelligence quotient (IQ) were used to assess psychologic effects. No correlation was found between oxygenation and the IQ. More recent research[2,3] has suggested that multiple clinical criteria of perinatal asphyxia may have more prognostic value than a measure of oxygen content in neonatal blood alone. In addition, at the time of the first follow-up study, the children in the sample were too young to have special experimental psychologic tests[4] of brain damage administered. The present study includes other clinical criteria of perinatal asphyxia in addition to oxygen content of neonatal blood. Experimental psychologic tests of brain damage are used as well as the IQ test.

Prior to the present series, numerous retrospective[5–10] and prospective[2,3,11–18] studies on the psychologic effects of early asphyxia had appeared. Retrospective studies, while they generally agreed in showing a significant effect of early asphyxia, cannot answer the question of prognosis for the asphyxiated infant. In addition, they are often hampered by inadequate records of early asphyxia. Prospective studies, on the other hand, have produced conflicting findings. Some have shown a deleterious effect of early asphyxia,[3,11–15] while others have not.[16–18]

SUBJECTS

From April 1948 to August 1950, 404 newborns were selected at random from the ward service of Sloane Hospital for Women. Data on perinatal complications and samples of heel blood were collected for each subject, as previously described.[1] From April to December 1957, all subjects were recalled to the hospital by mail for their most recent psychologic testing. Table I shows the follow-up status of the original sample. Of 159 subjects available for testing in 1957, 3 had to be excluded, 2 because of brain damage subsequent to the neonatal period.* and 1 because of microcephalia. The latter was the only subject with gross neurologic signs, or possible congenital defect, in the available sample. The final sample for the present study numbered 156 children.

CRITERIA OF ASPHYXIA

Perinatal Complications

Prenatal, delivery, and neonatal complications were recorded for each subject.[1] From these data, several categories of perinatal complications were formed.

OBSTETRICAL: These complications are defined by the fetal anoxia scale of Graham *et al.*[14]

PREMATURITY: Infants whose birth weight was less than 2,500 gm were considered premature.

NEONATAL: Such complications were further categorized by the necessity for administration of *prolonged* or *essential* resuscitation. Resuscitation was considered prolonged if it was administered for more than 5 minutes, regard-

* One subject had questionable meningitis during the first year; the second sustained head trauma during childhood, after which pathologic electroencephalographic findings were noted.

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TABLE I

FOLLOW-UP STATUS OF ORIGINAL SAMPLE

	No. of Subjects
Letters returned	136
Letters unanswered	75
Unable to participate	25
Known dead	5
Known institutionalized	2
Known adopted	2
Available for testing	159
Total	404

less of whether oxygen was provided by a face mask or under pressure. Resuscitation was considered essential if oxygen was administered under pressure and if the record showed one of the following signs of poor clinical condition: 1) crying delayed for more than 2 minutes; 2) breathing inadequate for more than 2 minutes; 3) poor general condition including sleepiness, poor reflexes, etc.; and 4) excessive maternal medication; or if oxygen was administered by facial mask and the record showed two of the four signs of poor clinical condition.

MULTIPLE: This term was used when more than one of the three preceding categories of complications were noted.

All ratings and selections were made without knowledge of the results on psychologic tests. Table II shows the number of subjects within each category. It can be seen that 60 subjects had perinatal complications, while 96 did not.

TABLE II

NUMBER OF SUBJECTS IN EACH SUB-GROUP

*Complicated**		*Uncomplicated**	
Neonatal	29	Oxygen content groups	
		Low-High	21
Obstetrical	20	High-Low	17
		Low-Low	20
Premature	6	High-High	23
Multiple	5	Blood samples invalid	15
Totals	60		96

* In Tables II through VII, Complicated = those subjects having perinatal complications (see text); Uncomplicated = those subjects who had no complications in the perinatal period.

Oxygen Content of Blood

An average of 3.9 blood samples per subject was collected from 1 minute to 3 hours after birth. The mean oxygen content, derived from these samples, rose steadily from 6.1 vol. % for 1-5 minutes of life to 19.61 vol. % for 1-3 hours. The oxygen content of each subject was expressed in relation to this rising curve. Though not all subjects were sampled at the same time intervals, all but a few were sampled between 10 and 15 minutes after birth and also at 1 to 3 hours. Therefore, the oxygen content of each subject could be expressed as a deviation from the median content at 10 to 15 minutes and again at 1 to 3 hours.

Four sub-groups were formed on the basis of oxygen content: 1) Low-High: subjects below the median at 10 to 15 min, but above the median at 1 to 3 hr; 2) High-Low: above the median at 10 to 15 min, below the median at 1 to 3 hr; 3) Low-Low: below the median at both intervals; 4) High-High: above the median at both intervals. When the subject had no blood sample at 10 to 15 min or at 1 to 3 hr, a 1- to 10-min sample was substituted for the former, and a 30- to 60-min sample was substituted for the latter. Substitutions were required in 13 cases.

To study the effect of oxygen content, only subjects with no perinatal complications were used. The number in each sub-group is shown in Table II. It can be seen that 15 subjects with no complications had invalid blood samples.* While these subjects could not be used to study effects of oxygen content, they were used in comparing complicated with uncomplicated subjects.

PSYCHOLOGIC TESTS AND SIGNS

The battery of psychologic tests included both an IQ test and a representative sample of special tests for brain damage in childhood. Representative sampling of the special tests seemed necessary because they were all experimental tools, with incomplete standardiza-

* Two blood samples were spoiled. An additional 13 samples were considered invalid because they were obtained from subjects who were given brief oxygen administration, though they were in excellent clinical condition. It was thought that the oxygen administration would elevate the oxygen content in the blood samples for these subjects.

tion, varying clinical usage, and no adequate criteria for selecting among them.[4] Thus, the final battery included tests which are said to measure general ability, abstract ability, perceptual functioning, visuo-motor co-ordination, memory, attention span and emotional control —all purported to be vulnerable to brain damage.[4]

The tests were administered individually in uniform order, by a single psychologist, during a 2- to 3-hour session. Information on asphyxia was withheld from the tester until all subjects were tested. The following psychologic tests and signs were used:

IQ Test

WECHSLER INTELLIGENCE SCALE FOR CHILDREN (WISC):[19]

1) WISC Full Scale IQ

2) WISC Verbal Scale IQ minus Performance Scale IQ[20]

3) Wechsler Mental Deterioration Index[21]

4) Hewson's signs for brain damage[22]

5) Average score of WISC sub-tests minus score of WISC Block Design sub-test[4]

6) Average score of WISC sub-tests minus score of WISC Mazes sub-test[4]

7) Average score of WISC sub-tests minus score of WISC Coding sub-test[4]

Special Experimental Tests

BENDER-GESTALT TEST:[23]

8) Total Distortions[23]

9) Brain Damage Distortions[24]

10) Memory for Designs[4]

SORTING TEST:[25, 26]

11) Number of Irrelevant Explanations

12) Number of Unusual Selections

GOODENOUGH IQ TEST:[27]

13) WISC IQ minus Goodenough IQ[28]

FIGURE-GROUND TEST:[29]

14) Number of Correct Figures[30]

15) Number of Background Responses[30]

MARBLE BOARD TEST:[25, 29, 30]

16) Accuracy of Reproductions[31]

17) Manner of Approach[31]

RORSCHACH: Based on Piotrowski,[32] Ames,[33] and Werner,[34] the following Rorschach scores were selected to detect brain damage: R < 8, M + FM < 1, 1 Cn or C, M:C = 1:3 or more, F+ % < 70, 1 0—, 1 Do, 2 Ss, Perseveration, Impotence, Perplexity, Automatic Phrases.

18) Number of such Rorschach scores.

CRITICAL FLICKER FREQUENCY:[35]

19) Mean Critical Flicker Frequency[36]

BEHAVIOR RATINGS: Fels[37] ten-point rating scales of attention, emotional control and activity were used for each subject. If the subject obtained an extreme score on any of these scales, he was scored one point.

20) Mother Ratings: Number of extreme scores rated by mother.

21) Psychologist Ratings: Number of extreme scores rated by psychologist.

Report Card

The report card was rated for academic and social behavior, with 0 = A to B or Satisfactory; 1 = B— to C— or Needs Improvement; 2 = D and below or Unsatisfactory.

22) Social-Sum of subject's social ratings divided by number of ratings.

23) Academic-Sum of subject's academic ratings divided by number of ratings.

COMPARISON OF GROUPS

Table III shows that the group with perinatal complications (hereafter referred to as the complicated group) (see Table II) did not differ significantly from the group without perinatal complications (uncomplicated group) with regard to age, sex, or race. In addition, inquiries were made about each subject's vision. When a subject refused to wear prescribed glasses, forgot to bring them, or had other uncorrected visual defects, his scores on psychologic tests requiring vision were omitted from the sample. Furthermore, subjects who did not speak English were not given tests requiring comprehension of English language.

TABLE III

AGE, SEX AND RACE CHARACTERISTICS OF SAMPLE

Characteristic	*Complicated*	*Uncomplicated*	*Statistical Test*
Age (months)			
Mean	100.8	100.2	t= .73*
Sigma	8.2	7.3	
Sex (frequency)			
Male	29	56	χ^2=1.49*
Female	31	40	
Race (frequency)			
White	22	37	χ^2= .30*
Negro	33	49	
Puerto Rican and Oriental	5	10	

* Not significant.

Finally, the 159* subjects available for testing were compared with the remainder of the original 404 subjects. It was found that the proportion of subjects with perinatal complications was 39% for the available subjects and 53% for the unavailable. The 14% difference was significant at the 0.01 level ($\chi^2 = 8.10$), indicating that the available sample was relatively healthy. Some of the unavailable subjects may have died or been institutionalized because of perinatal complications. Whatever the case, any effects of perinatal asphyxia found in the present, relatively healthy sample, might have been larger for the total original sample.

STATISTICAL PROCEDURES

When a diagnostic sign was normally distributed, analysis of variance and t-tests were used to compare means. When a sign was distributed in a J-curve, chi-square was used either to compare the number of subjects falling below and above the median score, or to compare the number of subjects showing no sign with the number falling below and above the median score. Because there were 23 diagnostic signs, and because of the possibility of interdependence of signs, a significance level of 0.01 was required. "One tail tests of significance" were used, since it was predicted that asphyxia would have deleterious psychologic consequences.

RESULTS

Perinatal Complications

Positive Findings: The complicated group was significantly impaired on four psychologic tests and five diagnostic signs (Tables IV-VII).

IQ Test. Table IV provides the data to compare the mean IQs of subjects with and without perinatal complications. It can be seen that the mean IQ of the complicated group was 4.87 points lower than that of the uncomplicated group (significant difference at the 0.01 level). A second comparison was carried out, omitting the six premature subjects from the complicated group.* The results were almost identical. The complicated group showed a mean IQ 4.85 points lower than the uncomplicated group (significant at the 0.01 level).

TABLE IV

Comparison of Mean IQs for Complicated and Uncomplicated Groups

IQ	*Complicated*	*Uncomplicated*
Mean	94.88	99.75
Sigma	10.47	12.24
Number	58*	92*
	t=2.59	
	p= .01	

* Six subjects excluded because of visual or English-language handicap.

Finally, the mean IQs were compared for all four categories of complications: neonatal, obstetrical, premature and multiple. The differences among the means was not significant ($F = .27$), indicating that all complications were equally deleterious. The fact that the sample with multiple complications did not show a significantly greater reduction of scores may be related to the small size (five subjects) of this sample.

Special Experimental Tests. The complicated group was impaired on the Bender-Gestalt test (Table V). This test requires the subject to reproduce geometric figures. Distortions of the figures provide two diagnostic signs of brain damage: 1) Total Distortions, scoring all possible deviations from the original drawings;[23] and 2) Brain Damage Distortions, scoring those deviations occurring with brain damage.[24]

For the Total Distortions sign, in Table V is given the incidence of subjects with *few* distortions, less than the median number for the present sample, and with *many* distortions, more than the median number for the sample. No subject had no distortions at all. It can be seen that the incidence of many distortions was higher among complicated subjects than among the un-

* Comparison of the sample available for testing and the original sample includes the three subjects who were excluded from psychologic testing because of possible central nervous system infection, head trauma and microcephalia.

* Premature subjects were analyzed separately because they were a homogeneous clinical group.

TABLE V

BENDER-GESTALT TEST: INCIDENCE OF COMPLICATED AND UNCOMPLICATED SUBJECTS SHOWING NO, FEW, AND MANY DISTORTIONS

Number of Distortions	*Per Cent Incidence of Subjects**	
	Complicated	*Uncomplicated*
Total Distortions		
None	0	0
Few**	38	58
Many	62	42
	$\chi^2 = 5.79$	
	$p = .01$	
Brain Damage Distortions		
None	22	21
Few	24	54
Many	54	25
	$\chi^2 = 15.64$	
	$p = .01$	

* Five subjects excluded for visual defects.
** Few = less than the median number.
Many = more than the median number.

complicated. The difference between the complicated and uncomplicated groups was significant at the 0.01 level. An additional statistical test, omitting the prematures from the complicated group, showed results in the same direction with a significance value of 0.025.

For the Brain Damage Distortions sign, the incidence of subjects with no, few and many distortions is given in Table V. *Few* and *many* are defined again, in terms of the median number for the present sample. It can be seen that the incidence of many distortions was higher among complicated subjects than among the uncomplicated. The difference between the complicated and uncomplicated groups was significant at the 0.01 level. An additional statistical test, omitting the prematures, showed results in the same direction with a significance value of 0.01.

The complicated group was impaired on the Sorting test (Table VI). This test requires the subject to select which of three objects "goes best" with a given object. Usual Selections, made by the majority of subjects, are based on similarity of function, class, form or color. Unusual Selections provide a diagnostic sign of brain damage.[25, 26] The incidence of subjects with no, few, or many Unusual Selections is shown in Table VI. It can be seen that the incidence of many Unusual Selections was higher among complicated subjects than among the uncomplicated. The difference between the complicated and uncomplicated groups was significant at the 0.01 level. An additional statistical test, omitting the prematures from the complicated group, showed results in the same direction with a significance value of 0.01.

The complicated group was impaired on the Critical Flicker Frequency test (Table VII). This test requires the subject to indicate the point where a flickering light of variable rate appears to fuse. The diagnostic sign of brain damage is stated in terms of the number of flickers per second at the point of fusion.[35] Subjects with brain damage fuse at a lower flicker rate. The complicated group fused at a significantly lower flicker frequency than the uncomplicated group. Only 26 subjects were tested because of unavoidable delays in obtaining equipment. There were no prematures in this sample.

To recapitulate, complicated subjects, compared to the uncomplicated, show a significantly lower mean IQ; significantly more distortions on the Bender-Gestalt test; significantly more unusual selections on the

TABLE VI

SORTING TEST: INCIDENCE OF COMPLICATED AND UNCOMPLICATED SUBJECTS SHOWING NO, FEW, AND MANY UNUSUAL SELECTIONS

Number of Unusual Selections	*Per Cent Incidence of Subjects*	
	Complicated	*Uncomplicated*
None	32	24
Few*	38	64
Many	30	12
	$\chi^2 = 11.03$	
	$p = .01$	

* Few = less than the median number.
Many = more than the median number.

TABLE VII

COMPARISON OF MEAN CRITICAL FLICKER FREQUENCY FOR COMPLICATED AND UNCOMPLICATED GROUPS

Flicker Frequency	*Complicated*	*Uncomplicated*
Mean	33.03	36.73
Sigma	4.23	2.17
Number	13	13
	t=2.77	
	p= .01	

Sorting test; and a significantly lower mean critical flicker frequency.

Abilities which the Tests Measure. While the IQ is a measure of general ability, the Bender-Gestalt, Sorting, and Critical Flicker Frequency tests are said to measure specific abilities vulnerable to brain damage. However, the three special tests all correlated significantly with IQ (Table VIII), indicating that they also reflected general ability. Since the complicated and uncomplicated groups differed in general ability, it was necessary to control for IQ before attributing special disabilities to asphyxia. Using children of average IQ (90 to 110), the three special tests were re-analyzed for their ability to discriminate between complicated and uncomplicated subjects. Data in Table IX show that all but the Bender-Gestalt Total Distortions sign maintained discriminating power. Even without the Bender-Gestalt sign, all three special tests provided at least one sign which discriminated between the complicated and uncomplicated groups.

The positive findings would seem to suggest that the complicated group was not only impaired in general ability, but also had specific disabilities, measured by the three special tests. The Bender-Gestalt is said to measure visuo-motor co-ordination; the Sorting test, abstract ability; and the Critical Flicker Frequency, a perceptual function.[4]

TABLE VIII

CORRELATIONS OF SPECIAL TESTS WITH IQ

Special Test	*No.*	*Correlation*	*p*
Bender-Gestalt			
Total distortions	150	−.51	.01
Brain damage distortions	150	−.56	.01
Sorting—unusual selections	150	−.40	.01
Critical flicker frequency	26	+.52	.01

TABLE IX

RE-ANALYSIS OF SPECIAL TESTS FOR CHILDREN OF AVERAGE I.Q.

Special Test	*Number*	*Statistical Test*	p
Bender-Gestalt			
Total distortions	93	χ^2= .001	.99
Brain damage distortions	93	χ^2= 9.63	.01
Sorting—unusual selections	96	χ^2=14.07	.01
Critical flicker frequency	15	t= 2.71	.01

NEGATIVE FINDINGS: Before evaluating the clinical significance of the positive findings, negative findings must be examined. The results show no significant differences between complicated and uncomplicated subjects on the remaining 6 experimental tests and 18 diagnostic signs. Among the negative signs are many that purport to measure the same functions as those signs providing positive findings. Visuo-motor co-ordination is said to be measured by diagnostic signs 2 through 7, 13, 16, and 17; abstract ability by signs 3, 5 and 11; and perceptual functioning by signs 13, 14, 15 and 18 (see section on Psychologic Tests). Whether the tests showing positive results are more sensitive instruments, or whether they measure somewhat different functions, is not known. In either case, caution must be exercised in interpreting the clinical significance of the positive findings.

Oxygen Content of Blood

None of the 23 diagnostic signs showed statistically significant differences among the four sub-groups with varying oxygen content.

DISCUSSION

Perinatal Complications

The positive findings would appear to support previous results showing a significant effect of early asphyxia.[3, 5–15] However, the clinical significance of the data on the

special tests appears to be ambiguous. In addition, the small though statistically significant impairment of 4.87 points in IQ for the complicated subjects is of questionable clinical significance. At best, an attempt can be made to examine the conflicting findings of the past and present research, with a view to further investigation.

CRITERIA OF PERINATAL ASPHYXIA: The present study uses a broad clinical definition of perinatal asphyxia. There were four categories of complications, and a large variety of problems was considered within each category. In contrast, several previous studies have used relatively narrow clinical definitions of perinatal asphyxia, such as apnea neonatorum of 1 to 3 minutes duration.[12,16-18] The accumulated research indicates that the broad definition[11,13-15] is more likely to show a significant effect of perinatal asphyxia than the narrow one.[16-18] This suggests that the crucial deleterious perinatal factors have not as yet been isolated, and that further study is necessary.

PSYCHOLOGIC SIGNS: The statistically significant findings on the special tests of brain damage suggest that some of these tests, with further refinements, may be fruitful in detecting effects of early asphyxia. The Critical Flicker Frequency test seems particularly promising, as it yielded significant results with a small sample of 26 subjects. It should be noted that, except for two studies using behavior ratings,[15,17] and one using drawings of geometric figures,[11] previous research in this area has been limited to the IQ test alone. In addition, the accumulated research suggests that individual IQ tests[11-15] are more apt to show an effect of early asphyxia than are group IQ tests.[16-17]

EXPERIMENTAL CONTROLS: Graham *et al.*[3] suggest that conflicting previous findings may be due to variations in the number and kind of controlled variables. Eight variables were controlled in the present study:

race	visual defects
age	language defects
sex	gross neurologic defects
post-neonatal brain trauma	congenital defects

Although none of the previous studies has controlled all these factors, Darke[12] found impressive IQ differences with a small sample of children with perinatal asphyxia, using their normal siblings as controls. It is possible that a similar control for hereditary factors in IQ may have enlarged the small IQ difference shown by the present sample.

Finally, it seems possible to control the complicated sample too rigidly. While several studies,[16,17] including the present one, eliminated subjects with gross neurologic difficulties from their complicated samples, Usdin and Weil[18] excluded subjects showing any neurologic signs at birth or at the time of follow-up. It may be that they thereby also eliminated subjects with impaired psychologic abilities. It can be seen that the experimental conditions of the prospective studies vary considerably. Further research is necessary to explore what seem to be the significant conditions.

Oxygen Content of Blood

The finding of no relationship between oxygen content in neonatal blood and the psychologic tests agrees with previous results.[1,2] Inasmuch as multiple clinical criteria of perinatal asphyxia correlate with later psychologic function, while measurement of oxygen content does not, it seems that the latter may not adequately reflect early asphyxia. In fact, since 1948, when the samples of heel blood for the present study were collected, numerous limitations of the determination of oxygen content have been noted: 1) Oxygen levels in the blood in the neonate have been shown to be highly variable, falling or rising significantly in less than 5 minutes;[1] 2) it has been found that oxygen content of peripheral blood samples depends on local circulatory conditions, and may not adequately represent the arterial blood supplying the brain;[38] 3) it has been demonstrated that the ductus arteriosus is patent for some time after birth,[39,40] so that crying may result in a considerable shunting of venous blood into arterial circulation.[41,42]

Because of the limitations in the tech-

niques for determination of oxygen content in heel blood, research efforts have been directed to uncovering other biochemical indicators of early asphyxia. The recent work of James *et al.*[43,44] suggests that arterial pH and degree of metabolic acidosis may provide some estimate of the length of insult from asphyxia. Further investigation seems indicated.

SUMMARY AND CONCLUSIONS

A prospective study on the psychologic effects of perinatal asphyxia is reported. It is the second report of follow-up studies of a sample of newborns selected at random from an obstetrical ward service in New York City. The first study showed no effect of early asphyxia as measured by oxygen content of heel blood in the neonatal period. Further investigation seemed indicated, using more extensive measures both of early asphyxia and psychologic effects.

In the present study, early asphyxia was defined by perinatal complications and by level of oxygen content in neonatal blood. Psychologic evaluation included 23 diagnostic signs of brain damage based on an IQ test, special experimental tests of brain damage, school report cards, and behavior ratings.

Children with perinatal complications showed a statistically significant decrement on the IQ test and on three special tests of brain damage: the Bender-Gestalt, Sorting test, and Critical Flicker Frequency. However, the clinical significance of these positive findings must be viewed with caution in the light of the relatively small mean decrement of 4.87 points in IQ and the negative findings on the remaining special tests of brain damage. A discussion of the conflicting results of the present and past research yielded suggestions for refinements in the clinical criteria of perinatal asphyxia, the psychologic instruments, and the selection of experimental controls.

While statistically significant relationships were demonstrated between multiple clinical criteria of perinatal asphyxia and several psychologic signs of brain damage in childhood, no such relationships were shown for the measurements of oxygen content in neonatal blood. The limitations of measurement of oxygen content are discussed together with suggestions for future research.

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